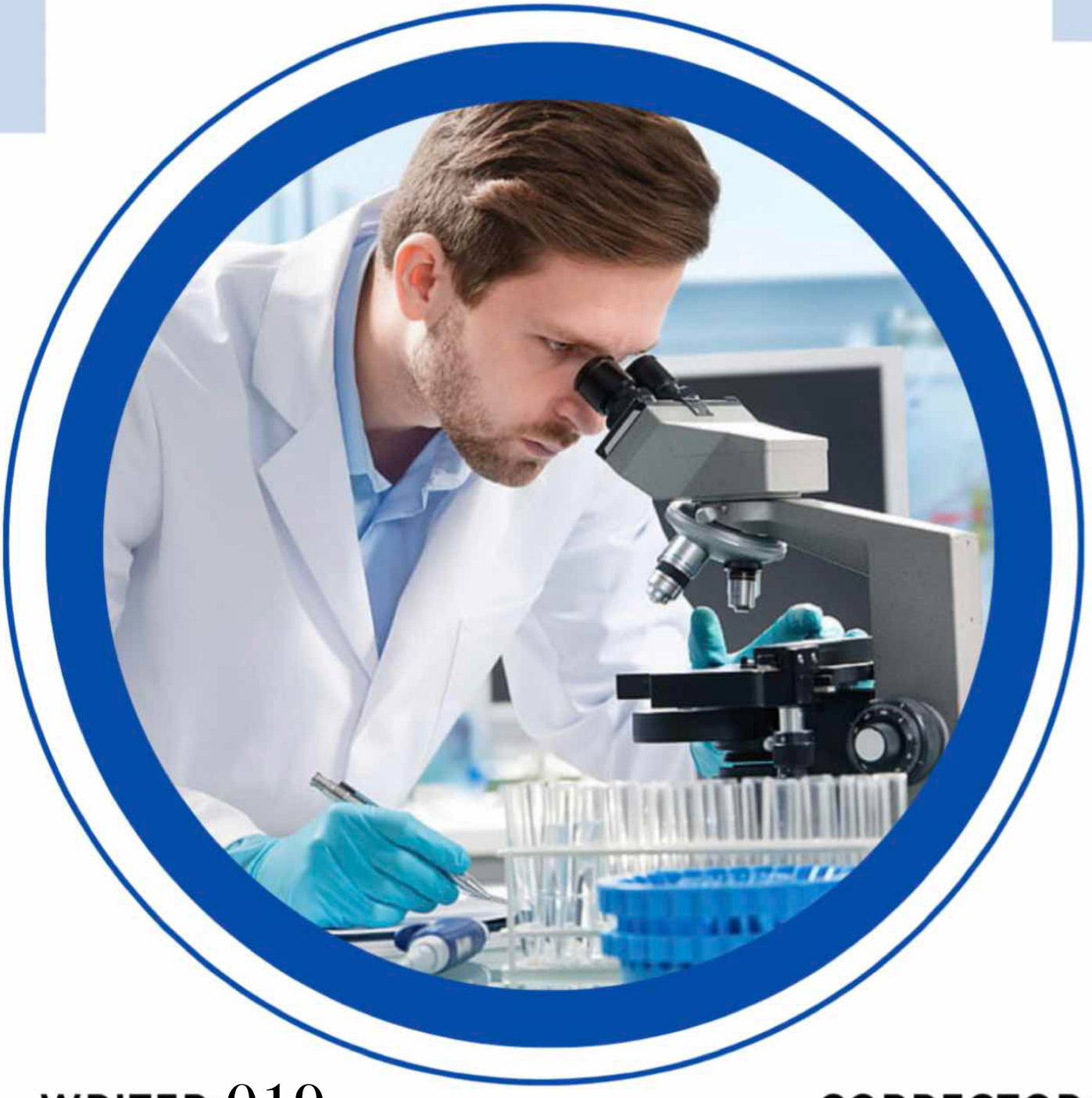
GI
PATHOLOGY

#4



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*Hey guys, long time no see ^^*
Welcome to sheet 4 where we will discuss some liver problems. Have fun

❶ Autoimmune Hepatitis

General Information

- It is chronic hepatitis with immunologic abnormalities.
- Its histologic features are similar to chronic viral hepatitis.
- It can have either an indolent or a severe course. In severe form it may lead to cirrohsis
- It is characterized by dramatic response to immunosuppressive therapy. Therefore, we need to differentiate between different causes chronic hepatitis as the treatments vary. Otherwise , [if we treated autoimmune hepatities as viral hepatitis]the condition will get worse

Features

Note that it's really hard to treat autoimmune hepatitis and in some cases it needs alot of time

- Classically, it is a disease of females with a predominance of 70% (about 70% of patients are females). Both females& males can have this disease but like any other immune desiese it's more common in females
- Usually patients show negative serology for viral antigens. So, no viral antigens are found in his blood. By this we can exclude viral hepatitis in most cases
- Patients have increased serum levels of Immunoglobulins (more than 2.5g/dL). High titers of autoantibodies are also found in about 80% of cases). Note that in most cases not all cases .
- Most patients (about 60%) can have other autoimmune diseases such as Rheumatoid Arthritis, Thyroiditis, Sjogren syndrome, or Ulcerative Colitis.

Types of Autoantibodies

These are antibodies that attack self-antigens and cells. They include:

- Anti-smooth muscles antibodies. These antibodies attack proteins inside our smooth muscles such as: Troponin, Tropomyosin, and Actin.

- liver/kidney microsomal antibodies. These antibodies attack proteins such as cytochrome p450 components and UDP-glucuronosyltransferase enzymes.
- Antibodies that attack soluble liver and pancreatic antigens.

Outcomes

- Mild to severe chronic hepatitis.
- Full remission in these patients is unusual :(In most autoimmune desises because the mechanism persists
- There is a small risk of cirrhosis (about 5%) but **it is probably the main cause of death.**

❷ Non-alcoholic Fatty Liver Disease (NAFLD)

It is now an important disease of the liver and has two types.

Types

- Steatosis (Fatty liver). Mild form usually not related to cirhosis
- Steatohepatitis. Note the -itis, it is associated hepatocyte destruction, parenchymal inflammation and progressive paracellular fibrosis.

In either way we have to know the underlying cause to avoid cirrhosis.

Predisposing factors

Most common predisposing factors for NAFLD include:

- Type II diabetes.
- Obesity. Caucasians with a BMI of 30 or higher and Asians with 25 or higher are considered obese

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Extra: You can use the following formula to calculate your body mass index (BMI).
BMI= mass in kg / (height in meters)²

- Dyslipidemia: Increase in Triglycerides and LDL (low density lipoprotein)
  Decrease in HDL (high density lipoprotein)
- Hypertension **(Extra Info)**

Pathogenesis

Fat accumulation in the liver can be due to a metabolic syndrome such as: Insulin Resistance, Obesity, and Dyslipidemia.
Any mechanism that is associated with an increase in the fatty acids in circulation can result in deposition of fat in the liver. These mechanisms include:

- Impaired oxidation of fatty acids.
- Increased synthesis and uptake of free fatty acids.
- Decreased hepatic secretion of VLDL (very low-density lipoproteins). Remember that VLDL is the carrier of fatty acids to target organs so they can utilize them.
- Activation and release of TNF, IL-6, and other chemokines (possibly due to direct or indirect effects of lipid) cause liver inflammation and damage.

Clinical Presentation

- NAFLD is the most common cause of incidental increase in transaminases in liver function test.
- Most patients are asymptomatic or have non-specific symptoms as Fatigue, Malaise and Right Upper Quadrant Discomfort.
- **Sometimes, severe symptoms are present.**
- Liver biopsy is required for definitive diagnosis.
- NAFLD might be a significant contributor to cryptogenic cirrhosis.

After taking the biopsy we score it depending on the amount of fat present ,cell damage , fibrosis out of 18 to deciede the severity of the desiese

❸ Hemochromatosis

It is a metabolic disease characterized by excessive accumulation of body iron (liver & pancreas) and can be primary or secondary (genetic or acquired).

Classical form in liver and pancreas but it can occur in any part of the body ex. skin ...etc.

In general terms Both primary and secendory iron accumilation is called hemochromatosis but clinically we call the primary hemochromatosis and the secondary is called siderosis

Causes of Acquired hemosidrosis

- Multiple transfusions — Multible blood transfusions when you're giving the patient blood you'rebcactully giving him red blood cells and as we know red cells' life span is short so they rapture and iron accumelates in the body to avoid this, patients that are under this condition are usually given some agents to avoid iron deposition
- ineffective erythropoiesis (thalassemia) — Premature rapture of Red blood cells before they are released to circulation
- increased iron intake (Bantu sidrosis)
- chronic liver disease

Features

- Micronodular cirrhosis (all patients)
- D.M (75 – 80%) Due to distruction of islets cells
- Skin prigmentation (75-80%) Due to iron deposition in subcutaneous tissue
- Cardiomegaly, joints disease, testicular atrophy
- Symptoms appear 5th – 6th decades and not before age 40 — Although it might be genetic, it needs time
- Male : Female ratio is 5-7 : 1. **EXTRA EXPLANATION:** menstrual bleeding in women limits the accumulation of iron until menopause. — In men it also appears earlier
- Genetic hemochromatosis has 4 variants. The most common form is autosomal recessive disease of adult onset caused by mutation in the HFE gene on chromosome 6 — The doctor said in the lecture chromosome 7, I guess by mistake 🤷‍♀️

Pathogenesis

- Primary defect in intestinal absorption of dietary iron. There is no excretory way of iron and the amount of iron presents in the body is controlled by regulating the site of iron absorption which is the proximal small intestine. Particularly dudenom
- Total body iron is 2-6g in adults in which 0.5g presents in the liver mostly in hepatocytes. In hemochromatosis, more than 50g Fe accumulate of which one-third presents in the liver. — Iron may be present in other sites such as bone marrow
- In herediatary hemochromatosis there is a defect in regulation of intestinal absorption of dietary iron leading to net iron accumulation of 0.5 – 1 g/yr. The gene responsible is HFE gene located on chr.6 close to HLA

gene complex.HFE gene regulates the level of hepcidin hormone synthesized in liver. This Hepcidin decreases iron absorption from intestine. So, HFE gene deletion causes iron overload.

Hepcidin synthetic process depends on the iron demand of the body when there is blood loss the hepcidin level decreases allowing more iron to be absorped and reach the circulation

Two mutation can occur in HFE gene:

- Mutation at 845 nucleotide → tyrosine substitution for cystine at AA 282 (C282 Y)
- Aspartate substitution for histidine at AA 63 (H63D)
- 10% of patients have other gene mutations
- Carrier rate for C282Y is 1/70
- Homozygosity is 1/200
- 80% of patients are homozygous for (C282Y) mutation & have the highest incidence of iron accumulation
- 10% of patients are either homozygous for H63D mutation or compound heterozygous for C282Y/H63D mutation

*Excessive Fe deposition causes toxicity of the tissues through: Lipid peroxidation, stimulation of collagen formation, and DNA damage.

Whatever the material is if it accumelates in the liver excessively it will lead to cell damage

Morphological Changes

- Deposition of hemosiderin in diffferent orgens like: Liver, Pancreas, Myocardium, Pituitary Adrenal Thyroid & parathyroid glands, Joints, and Skin
- Cirrhosis
- Pancreatic fibrosis
- No inflammation
- Fibrosis
- Cirrhosis
- Synovitis
- Polyarthritis(pseudogout)
- Pigmentation of liver
- fibrosis of pancreas & myocardium
- Atrophy of testes

Clinical Presentation

They need time to appear

- Hepatomegaly
- Abdominal pain
- Skin pigmentation
- Diabetes Miletus
- Cardiac dysfunction
- Atypical arthritis
- Hypogonadism with increased serum Fe ferritin
- Those with untreated disease, have a risk for HCC increased by 200-fold.

Good Luck!!